Case Report

Fibrodysplasia Ossificans Progressiva

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Abstract

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder of the connective tissue characterized by progressive disability as a result of extensive extra skeletal enchondral bone formation and malformed big toes which are often monophalangic. Occasional features include short thumbs, fifth finger clinodactyly, malformed cervical vertebrae and mild mental retardation.[1] Beginning during childhood, FOP progressively immobilizes all the joints through adult life, rendering movement impossible. Currently, there is no effective prevention or cure for this debilitating disease. Since it has an autosomal dominant inheritance, our concern is to highlight prompt genetic counseling in the concerned families although many sporadic cases have also been identified.

Keywords: Fibrodysplasia ossificans progressiva, Echondral bone.

Introduction

Fibrodysplasia ossificans progressiva is a progressive systemic disease. It is a rare condition with a prevalence of 1 case in 2 million. The hallmark of the disease is heterotrophic calcification of skeletal muscles and abnormalities of the big toes which may be the only abnormality present at birth. Occasional features include short thumbs, fifth finger clinodactyly, malformed cervical vertebrae, short broad femoral necks, deafness, scalp baldness, cardiac conduction defect and mild mental retardation.[1] The disease progresses to cause severe disability due to restriction of joints.

This case is presented here because of its rarity and to diagnose the condition early to minimise trauma and painful flare ups. In addition due genetic counselling to affected families should also be provided due to autosomal dominant inheritance.

Case Report

We report a case of a 9-year-old boy who presented with complaints of multiple abnormal bony projections arising from both his arms within the last 2 years. He had a history of trauma of his left arm from where the bony mass had appeared initially. A single mass gradually progressed to multiple such hard projections mainly involving the shafts of the long bones. There was no pain or tenderness in any of these masses. The child also had a congenital absence of great toes bilaterally with no dysmorphism. Previously one of this mass had been surgically excised but there have been recurrences in other areas. The child was a product of nonconsanguineous marriage, born to a 35 year old unaffected mother through a normal vaginal delivery and had normal developmental milestones. Family history was non supportive of any such illness. The boy had a short height for age and had developed joint contractures in both the elbow and knee joints causing inability to flex completely. Both his thumbs were contracted too with all his fingers medially rotated. His gait was normal but he could not attain a squatting posture completely. Spine was normal. Rest of neurological examination was unremarkable. The CBC showed microcytic, hypochromic anaemia with normal calcium, alkaline phosphatase and

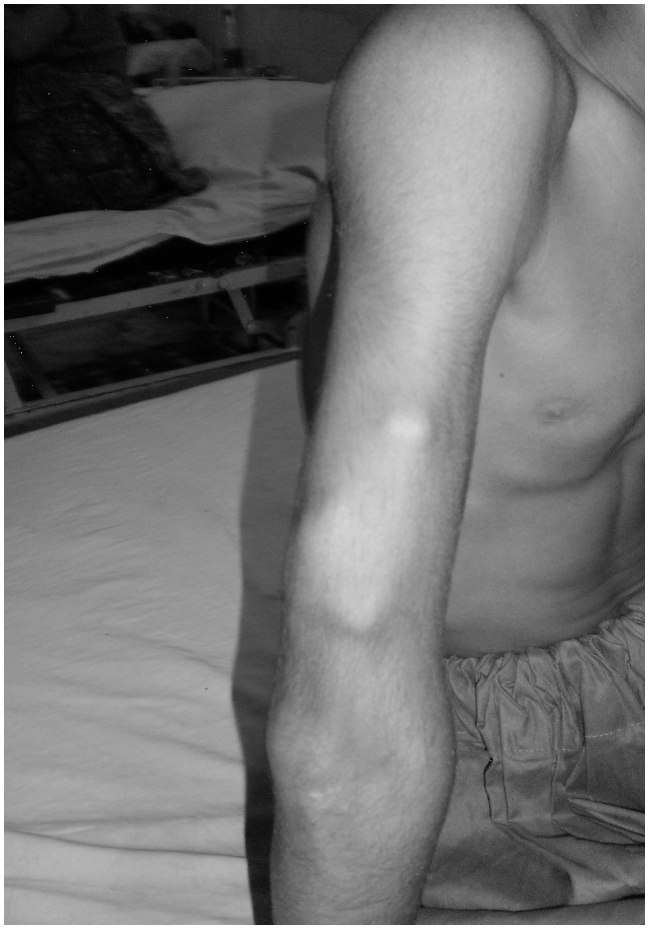

Figure-1.1: Multiple bony exostosis arising from the mid shaft of the right humerus.

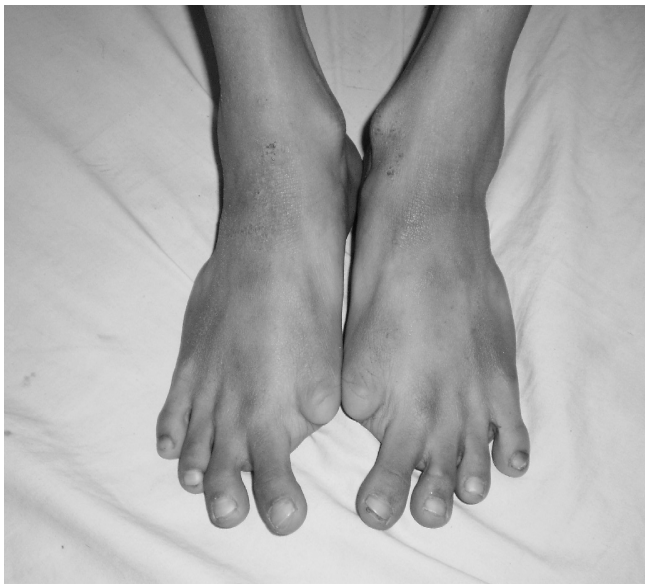

Figure-1.2: Cngenital absence of bilateral first metatarsals; a pathognomic sign of FOP.

other metabolic parameters. Skeletal survey revealed deformity of the phalanges and partial ankylosis of the 1st metacarpal joint. A bony exostosis was seen at the mid shaft of both clavicles. Furthermore bilateral ossification of muscles was noted along the middle lower shaft of both humeri and small bony projections along the inferior margin of the neck of femur, all highly suggestive of fibrodysplasia ossficans progressiva.

Discussion

Fibrodusplasia ossificans progressiva is inherited in an autosomal dominant pattern. New mutations of the gene are responsible for most of the cases The cause of FOP is a mutation in the bone morphogenetic protein type, receptor ACVRI, in chromosome 2.[2]

In our case the child was a 9 years old male but this disease affects both sexes equally. Majority of the cases present before 15 years of age. The condition is characterized by heterotopic calcification of the skeletal muscles and malformations of the big toe. In our case the boy had an absence of big toe since birth and now he presented with progressive restriction of movements that were associated with abnormal bony projections. This abnormal toe is present from birth and has been reported in 79-100% of patients which is considered as a pathognomonic sign.[3] Ossification usually starts in the neck, spine and shoulder girdle. This disease is known to spare anterior abdominal musculature, cardiac muscles and muscles of larynx and sphincters.[1,3] Involvement of the muscles is in the pattern of normal embryonic skeletal formation.

The patient presents with soft tissue swellings which may become painful. The child in the case discussed had no pain but his movements were apparently restricted. The episodes are triggered by trauma like injections and viral illnesses.[4] Inorder to delay the process of progression, our patient is to be kept on a regular follow up. Over time these swellings might progress distally, amplifying the risk for the patient of being confined to a wheel chair as it cannot be ceased. The acute episodes sometimes abate but majority of them result in bone formation in the muscles, ligaments and bones.

Involvement of muscles of mastication results in feeding difficulties and malnutrition. Jaw fixation is a key feature in this disease.[5] Extensive involvement of the muscles of the chest wall leads to a restrictive lung disease and death may occur due to pneumonia.[6]

Diagnosis is based on history and clinical involvement. Surgical excision is followed by recurrence and therefore biopsies should be avoided.

Radiographs are normal early in the course of illness. CT scan is sensitive to detect calcifications. Contrast enhancement CT+MRI can detect preosseous lesions of FOP and help in early diagnosis.[7]

The differential diagnosis considered in the case are Osteosarcoma, Aggressive juvenile fibromatosis and McCune Albright syndrome.

McCune Albright has it own features and endocrinal changes support the diagnosis. Osteosarcoma being extremely painful and having high levels of alkaline phosphatase needs detailed imaging of radiographs.

Frequently, FOP is misdiagnosed as Aggressive Juvenile fibromatosis, In aggressive fibromatosis, the lesions do not progress beyond the connective tissue growth phase, whereas in FOP, they mature through an endochondral process to form cartilage and bone. Biopsy revealing cartilage or bone cells in a lesion, excludes aggressive juvenile fibromatosis. Also, patients with aggressive juvenile fibromatosis do not have malformed toes supporting our diagnosis.

Biopsy might reveal a monocytic, lymphocytic infiltration into skeletal muscles followed by myocyte degeneration, fibroproliferation, chondrogenesis and osteogenesis.[8]

Laboratory investigations are normal.[7] Indomethicin, bisphosphnates, corticosteroids, single dose radiotherapy and bone marrow transplantation have all been tried.[9]

A recurrent mutation in the glycine-serine activation domain of the activin receptor IA/activin-like kinase-2, a bone morphogenetic protein type I receptor, was reported in all sporadic and familial cases of classic FOP.[10] The discovery of the FOP gene establishes a milestone in understanding this

disease. Effective therapies will be based on blocking activin-like kinase-2, a critical node in the BMP signaling pathway.

There is no supporting evidence of any parental inheritance in our case. Although, more than 95% cases are sporadic in origin by de novo mutations, having a pattern of autosomal dominant origin, there stays a 50% chance of inheritance in either of the sex.No prenatal diagnosis is yet available but the discovery of the FOP gene seems to be promising for future.

Conclusion

Fibrodysplasia ossificans progressive is a rare disesase.Early recognition of this autosomal dominant disorder is important for genetic counseling and minimizing trauma and painful flare ups.

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